IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1687
Flack *et al.*	Art Unit: 1614
Appl. No.: 10/806,088	Examiner: Anderson, James D.
Filed: March 22, 2004	Atty. Docket: 225011
For: **Gossypol for the Treatment of Cancer**	

Declaration of Jon Theodore Holmlund, M.D. under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jon Theodore Holmlund, M.D., declare and state:

1. I am Chief Medical Officer and Vice President at Ascenta Therapeutics, Inc., the licensee of the above-captioned application. A copy of my curriculum vitae and list of publications is attached hereto as Exhibit A.

2. I have read and understand the above-captioned application and its prosecution history, including the office action dated August 4, 2006. I understand that the examiner has rejected the pending claims of the application as not enabling the practice of the claimed methods for their full scope. In my opinion, it is expected and predictable that (-)-gossypol may be used to treat a wide diversity of cancers.

3. Recent findings support the expectation that (-)-gossypol is useful for the treatment of a wide diversity of cancers in humans. It has been reported that modulating apoptosis (programmed cell death) suppressing members of the Bcl-2 family holds potential for treating cancer. See Shore, G.C., and Vaillet, J., *American Society of Hematology* 226-230 (2005) (Exhibit B). Shore and Viallet report that such apoptosis

suppressors (Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and A1) are often strongly elevated in diverse cancers, and have the potential to confer resistance to endogenous cell death stimuli and many cancer treatments. Moreover, multiple pro-survival members are typically up-regulated in a given cancer. Thus, new compounds are being tested which antagonize multiple Bcl-2 family proteins and induce apoptosis. GX15-070, a small organic molecule which reportedly binds to Bcl-w, Bcl-xL and Mcl-1 with a K_D value in the 0.5 μM range, was found to exhibit antitumor activity as a single agent across diverse cancer cell types. (See pages 228-229 of Shore and Vaillet.) Thus, a small organic molecule which binds multiple Bcl-2 family members is expected to be useful for the treatment of diverse cancer cell types.

4. (-)-Gossypol binds to Bcl-2 and Bcl-xL with quite high affinities. (-)-Gossypol has K_i values of 320 nM and 480 nM to Bcl-2 and Bcl-xL proteins, respectively, in a competitive fluorescence polarization-based binding assay. A competitive binding assay showed that (-)-gossypol also binds to Mcl-1 protein, another anti-apoptotic Bcl-2 member, with a K_i of 180 nM. Thus, (-)-gossypol binds with high affinity to three apoptosis-suppressing members of the Bcl-2 family and, like GX15-070, is expected to be useful for the treatment of diverse cancer cell types.

5. (-)-Gossypol has been tested in the clinic for cancer treatment activity as a single agent in a clinical trial. As shown in Exhibit C, when (-)-gossypol (AT-101) was administered to patients with chronic lymphocytic leukemia (CLL),[1] activity was observed in terms of reduced cancer cell load in the peripheral blood (6 of 8 patients),

[1]In this study, CLL patients received a total dose of 30 or 40 mg of (-)-gossypol either once daily or in divided doses either every day or for 21 of 28 days for a maximum of 12 weeks.

lymph nodes (8 of 8 patients) and spleen (6 of 6 patients with an enlarged spleen). In addition, one patient exhibited an improved platelet count and 2 patients exhibited improved disease symptoms. While these patients were not cured, they most certainly have been treated.

6. (-) Gossypol is also being tested in the clinic for activity against prostate cancer. In an ongoing study, as of 24 August 2006, two of twenty-three patients treated have experienced partial responses of the tumor marker prostate specific antigen (PSA), an indicator of clinical activity. Five others have experienced at least some improvement in PSA levels. Ten patients remain on treatment, including the two with partial PSA responses, while the others have discontinued treatment for progressive cancer or other reasons. For those patients who exhibited a partial response, their prostate cancer was certainly treated."

7. In another study, 30 mg/day of (-)-gossypol was administered to a patient for the treatment of follicular lymphoma. As shown in Exhibit D, the patient experienced a 61% reduction in lesion size.[2] For this patient, the follicular lymphoma was certainly treated.

8. Additional evidence which supports the enablement of the present invention may be found in published U.S. Patent Application 20040214902, attached hereto as Exhibit E.

9. On page 5 of the Office Action, it is asserted that the claims are extremely broad insofar as they are directed to the treatment of different cancers with different

---

[2]In this study, the patient was treated with rituxamib for one year, then stopped. After about a month, the patient experienced progressive disease. The patient then

etiologies and treatment regimes. However, the breadth of the present claims is justified in view of what is known about strong elevation of the prosurvival Bcl-2 members in diverse cancer cell types, the fact that (-)-gossypol strongly binds to 3 members of this group, and the fact that (-)-gossypol has been found useful for the treatment of multiple types of cancer.

10. On pages 5-6 of the Office Action, it is asserted that no direction or guidance for the administration regimes necessary to treat all of the cancers with the various compounds are given. Further, it is asserted that the working examples are limited to the treatment of adrenal cancer with racemic gossypol and, thus, the Applicants have only provided specific direction or guidance for the treatment of adrenal cancer with racemic gossypol. I respectfully disagree with this assessment. Table 4 of the reissue application provides specific guidance as to dose ranges of (-)-gossypol (20-100 mg/day) that may be administered. These dose ranges encompass the doses of (-)-gossypol which have been found in practice (see above) to be useful for the treatment of various cancers with various etiologies by daily dosing as disclosed in the reissue application. Thus, the present application provides enough direction and guidance for one of ordinary skill in the art to practice the invention without undue experimentation.

11. The Office Action also alleges that the practice of the invention is unpredictable, and that the therapeutic index for gossypol is extremely narrow. As the above clinical studies indicate, the therapeutic index for (-)-gossypol is wide enough to allow for the treatment of a number of different cancers with different etiologies.

---

received (-) gossypol. SPD = the sum of the products of the greatest perpendicular diameter of the measured lesion (a measure of tumor volume). LN = lymph nodes.

12. In summary, all of the evidence to date provides the expectation that (-)-gossypol is useful for the treatment of diverse cancers. Accordingly, one of ordinary skill in the art would have every reason to expect that the method of treating cancers as claimed is enabled for its full scope.

13. I have read and understand 37 C.F.R § 10.18(b)

Respectfully submitted,

Signature 8/24/06
Date

CURRICULUM VITAE

NAME: Jon Theodore Holmlund, M.D.

EDUCATION: M.D., SUNY-Buffalo, 1984
B.A., Amherst College, 1979

MEDICAL LICENSURE: Maryland (D35450)—Inactive

SPECIALTY BOARD CERTIFICATION: Medical Oncology, 1991
Internal Medicine, 1987

BRIEF CHRONOLOGY OF EMPLOYMENT:

4/04-Date	Chief Medical Officer and Vice President, Development Ascenta Therapeutics, Inc. San Diego, CA
3/03-3/04	Vice President, Development Head of Clinical Development Isis Pharmaceuticals, Inc. Carlsbad, California
6/02-3/03	Vice President, Drug Development Isis Pharmaceuticals, Inc. Carlsbad, California
3/00-6/02	Executive Director, Drug Development Isis Pharmaceuticals, Inc. Carlsbad, California
1/98-3/00	Medical Director, Drug Development Isis Pharmaceuticals, Inc. Carlsbad, California
8/97-12/97	Associate Medical Director, Drug Development Isis Pharmaceuticals, Inc. Carlsbad, California
1/96-8/97	Senior Investigator Biological Resources Branch, Developmental Therapeutics Program, and Investigational Drug Branch, Cancer Therapy Evaluation Program Division of Cancer Treatment, Diagnosis, and Centers National Cancer Institute National Institutes of Health Frederick, Maryland and Rockville, Maryland

7/90-12/95	Project Officer, Program Director, and Senior Clinical Investigator Biological Resources Branch and Clinical Research Branch Biological Response Modifiers Program Division of Cancer Treatment National Cancer Institute National Institutes of Health Frederick, Maryland
7/88-6/90	Fellow in Hematology/Oncology George Washington University Medical Center Washington, D.C.
7/87-6/88	Instructor in Internal Medicine George Washington University Medical Center Washington, D.C.
7/84-6/87	Resident in Internal Medicine George Washington University Medical Center Washington, D.C.
7/81-6/82	Aide to Senator Pete V. Domenici (R-NM) United States Senate Washington, D.C.

PROFESSIONAL SOCIETIES: American Society of Clinical Oncology
American Association for Cancer Research
Christian Medical/Dental Society

HONORS/AWARDS: Sustained Superior Performance Award
Department of Cancer Treatment, Diagnosis, and Centers
National Cancer Institute
February 1997

Special Act or Service Award
Department of Cancer Treatment
National Cancer Institute
July 1992

COMMITTEES/OTHER ACTIVITIES:

Fall 1995-Spring 1997 — Core Courses in Biochemical Regulatory Engineering Program, University of Maryland, Baltimore County:

Regulatory Issues in Biotechnology	Fall 1995
Good Manufacturing Practices for Bio-Processes	Spring 1996
Quality Control and Quality Assurance of Biotechnology Products	Fall 1996
Biotechnology GMP Facility Design, Construction and Validation	Spring 1997

June 11-13, 1997 — "The Mechanics of Preparing INDs and NDAs and FDA Regulations"
Institute for Applied Pharmaceutical Sciences
Center for Professional Advancement
San Francisco, California

1994-1997 — Protocol Reviewer for Physician's Data Query

1991-1997 — Reviewer for Journal of the National Cancer Institute

1990-1997 — Biologics Operating Committee, DCTDC/NCI/NIH

1990-1997 — Decision Network Committee, DCTDC/NCI/NIH (AD HOC)

1991-1992 — Organizing Committee for FDA/NCI Workshop on Preclinical Safety Testing of Monoclonal Antibodies (January, 1992, Bethesda, Maryland)

1990-1992 — Clinical Research Panel, NCI/NIH Intramural Program (AD HOC)

ADDRESSES:

Office:
Ascenta Therapeutics Inc.
11455 El Camino Real
Suite 460
San Diego, CA
Phone: 858-436-1220
Fax: 858-436-1201
Cell: 858-736-7600
e-mail: jholmlund@ascenta.com

Residence:
1315 Cassins Street
Carlsbad, CA 92011

Phone: (760) 804-0590
e-mail: cmsharon@adelphia.net

BIBLIOGRAPHY
Jon T. Holmlund, M.D.

1. Advani R, Lum BL, Fisher GA, Halsey J, Geary RS, Holmlund JT, Kwoh TJ, Dorr FA, Sikic BI. A phase I trial of aprinocarsen (ISIS 3521/LY900003), an antisense inhibitor of protein kinase C-alpha administered as a 24-hour weekly infusion schedule in patients with advanced cancer. Invest New Drugs 23:467-477, 2005.

2. Grossman SA, Alavi JB, Supko JG, Carson KA, Priet R, Dorr FA, Grundy JS, Holmlund JT. Efficacy and toxicity of the antisense oligonucleotide aprinocarsen directed against protein kinase C-alpha delivered as a 21-day continuous intravenous infusion in patients with recurrent high-grade astrocytomas. Neuro-oncol 7:32-40, 2005.

3. Marshall JL, Eisenberg SG, Johnson MD, Hanfelt J, Dorr FA, El-Ashry D, Oberst M, Fuxman Y, Holmlund J, Malik S. A phase II trial of ISIS 3521 in patients with metastatic colorectal cancer. Clin Colorectal Cancer 4:268-274, 2004.

4. Villalona-Calero MA, Ritch P, Figueroa JA, Otterson GA, Belt R, Dow E, George S, Leonardo J, McCachren S, Miller GL, Modiano M, Valdivieso M, Geary R, Oliver JW, Holmlund J. A phase I/II study of LY900003, an antisense inhibitor of protein kinase C-alpha, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer. Clin Cancer Res 10(18 Pt 1):6086-6093, 2004.

5. Rao S, Watkins D, Cunningham D, Dunlop D, Johnson P, Selby P, Hancock BW, Fegan C, culligan D, Schey S, Morris TC, Lissitchkov T, Oliver JW, Holmlund JT. Phase II study of ISIS 3521, an antisense oligodeoxynucleotide to protein kinase C alpha, in patients with previously treated low-grade non-Hodgkin's lymphoma. Ann Oncol 15:1413-1418, 2004.

6. Holmlund JT. Applying antisense technology: Affinitak and other antisense oligonucleotides in clinical development. Ann N Y Acad Sci 1002:244-251, 2003.

7. Advani R, Peethambaram P, Lum BL, Fisher GA, Hartmann L, Long JH, Halsey J, Holmund JT, Dorr A, Sikic BI. A Phase II trial of aprinocarsen, an antisense oligonucleotide inhibitor of protein kinase C alpha, administered as a 21-day infusion to patients with advanced ovarian carcinoma. Cancer 100:321-326, 2004.

8. Oza AM, Elit L, Swenerton K, Faught W, Ghatage P, Carey M, McIntosh L, Dorr A, Holmlund JT, Eisenhauer E; NCIC Clinical Trials Group Study (NCIC IND.116). Phase II study of CGP 69846A (ISIS 5132) in recurrent epithelial ovarian cancer: an NCIC clinical trials group study (NCIC IND.116). Gynecol Oncol 89:129-133, 2003.

9. Adjei AA, Dy GK, Erlichman C, Reid JM, Sloan JA, Pitot HC, Alberts SR, Goldberg RM, Hanson LJ, Atherton PJ, Watanabe T, Geary RS, Holmlund J, Dorr FA. A phase I trial of ISIS 2503, an antisense inhibitor of H-ras, in combination with gemcitabine in patients with advanced cancer. Clin Cancer Res 9:115-123, 2003.

10. Mani S, Rudin CM, Kunkel K, Holmlund JT, Geary RS, Kindler HL, Dorr FA, Ratain MJ. Phase I clinical and pharmacokinetic study of protein kinase C-alpha antisense oligonucleotide ISIS 3521 administered in combination with 5-fluorouracil and leucovorin in patients with advanced cancer. Clin Cancer Res 8:1042-1048, 2002.

11. Cripps MC, Figueredo AT, Oza AM, Taylor MJ, Fields AL, Holmlund JT, McIntosh LW, Geary RS, Eisenhauer EA. Phase II Randomized Study of ISIS 3521 and ISIS 5132 in Patients with Locally Advanced or Metastatic Colorectal Cancer: A National Cancer Institute of Canada Clinical Trials Group Study. Clin Cancer Res 8:2188-2192, 2002.

12. Cunningham CC, Holmlund JT, Geary RS, Kwoh TJ, Dorr A, Johnston JF, Monia B, Nemunaitis J. A Phase I trial of H-ras antisense oligonucleotide ISIS 2503 administered as a continuous intravenous infusion in patients with advanced carcinoma. Cancer 92:1265-1271, 2001.

13. "Clinical Activities in Patients with Solid Tumors or Lymphoma," in: Crooke, ST, ed. Antisense Drug Technology: Principles, Strategies, and Applications. New York, Marcel Dekker, Inc. pp.739-760.

14. Rudin CM, Holmlund J, Fleming GF, et al. Phase I Trial of ISIS 5132, an antisense oligonucleotide inhibitor of c-raf-1, administered by 24-hour weekly infusion to patients with advanced cancer. Clin Cancer Res 7:1214-1220, 2001.

15. Cunningham CC, Holmlund JT, Schiller JH, Geary RS, Kwoh TJ, Dorr A, and Nemunaitis J. A phase I trial of c-*raf* kinase antisense oligonucleotide ISIS 5132 administered as a continuous intravenous infusion in patients with advanced cancer. Clin Cancer Res 6:1626-1631, 2000.

16. Holmlund JT, Monia BP, Kwoh TJ, and Dorr FA. Toward antisense oligonucleotide therapy for cancer: Isis compounds in clinical development. Curr Opin Molec Therapeutics 1:372-385, 1999.

17. Stevenson JP, Yao K-S, Gallagher M, Friedland D, Mitchell EP, Cassella A, Monia B, Yu R, Holmlund J, Dean N, Dorr FA, Geary R, and O'Dwyer PJ. Phase I clinical/pharmacokinetic and pharmacodynamic trial of the c-*raf*-1 antisense oligonucleotide ISIS 5132 (CGP 69846A). J Clin Oncol 17:2227-2236, 1999.

18. Nemunaitis J, Holmlund JT, Kraynak M, Richards D, Bruce J, Ognoskie N, Kwoh TJ, Geary R, Dorr A, Von Hoff D, and Eckhardt SG. Phase I evaluation of ISIS

3521 (ISI 641A), an antisense oligodeoxynucleotide to protein kinase C-α, in patients with advanced cancer. J Clin Oncol 17:3586-3595, 1999.

19. Yuen AR, Halsey J, Fisher GA, Holmlund JT, Geary RS, Kwoh TJ, Dorr A, and Sikic BI. Phase I study of an antisense oligonucleotide to protein kinase C-α (ISIS 3521/ISI 641A) in patients with cancer. Clin Cancer Res 5:3357-3363, 1999.

20. O'Dwyer PJ, Stevenson JP, Gallagher M, Cassella A, Vasilevskaya I, Monia BP, Holmlund J, Dorr FA, and Yao K-S. c-*raf*-1 Depletion and Tumor Responses in Patients Treated with the c-*raf*-1 Antisense Oligodeoxynucleotide ISIS 5132 (CGP 69846A). Clin Cancer Res 5:3977-3982, 1999.

21. Monia BP, Holmlund J, and Dorr FA. Antisense approaches for the treatment of cancer. Cancer Investigation 18:635-650, 2000.

22. Miller LL, Korn EL, Stevens DS, Janik JE, Gause BL, Kopp WC, Holmlund JT, Curti BD, Sznol M, Smith JW II, Urba WJ, Donegan SE, Watson TM, and Longo DL. Abrogation of the hematological and biological activities of the interleukin-3/granulocyte-macrophage colony-stimulating factor fusion protein PIXY321 by neutralizing anti-PIXY321 antibodies in cancer patients receiving high-dose carboplatin. Blood 93:3250-3258, 1999.

23. Dean NM, McKay RA, and Holmlund J. Antisense oligonucleotides as inhibitors of genes that regulate AP-1: pharmacology and clinical development. Antisense Nucl Acid Drug Devel 8:147-151, 1998.

24. Sznol M and Holmlund J. Antigen-specific agents in development. Semin Oncol 24:173-186, 1997.

25. Fenton RG, Steis RG, Madara K, Zea AH, Ochoa AC, Janik JE, Smith JW 2nd, Gause BL, Sharfman WH, Urba WJ, Hanna MG, DeJager RL, Coyne MX, Crouch RD, Gray P, Beveridge J, Creekmore SP, Holmlund J, Curti BD, Sznol M, and Longo DL. A phase I randomized study of subcutaneous adjuvant IL-2 in combination with an autologous tumor vaccine in patients with advanced renal cell carcinoma. J Immunother Emphasis Tumor Immunol 19:364-374, 1996.

26. Gause BL, Sznol M, Kopp WC, Janik JE, Smith JW 2nd, Steis RG, Urba WJ, Sharfman W, Fenton RG, Creekmore SP, Holmlund J, Conlon KC, VanderMolen LA, and Longo DL. Phase I study of subcutaneously administered interleukin-2 in combination with interferon alfa-2a in patients with advanced cancer. J Clin Oncol 14:2234-2241, 1996.

27. Curti BD, Ochoa AC, Urba WJ, Alvord WG, Kopp WC, Powers G, Hawk C, Creekmore SP, Gause BL, Janik JE, Holmlund JT, Kremers P, Fenton RG, Miller L, Sznol M, Smith JW 2nd, Sharfman WH, and Longo DL. Influence of interleukin-2 regimens on circulating populations of lymphocytes after adoptive

transfer of anti-CD-3-stimulated T cells: results fromm a phase I trial in cancer patients. J Immunother Emphasis Tumor Immunol 19:296-308, 1996.

28. Kopp WC and Holmlund JT. "Cytokines and Immunological Monitoring," in Pinedo HR, Longo DL, and Chabner BA (Eds.), Cancer Chemotherapy and Biological Response Modifiers, Annual 16, Amsterdam, Elsevier Science Publishers B.V., 1996, pp. 189-238.

29. Janik JE, Miller LL, Longo DL, Powers GC, Urba WJ, Kopp WC, Gause BL, Curti BD, Fenton RG, Oppenheim JJ, Conlon KC, Holmlund JT, Sznol M, Sharfman WH, Steis RG, Creekmore SP, Alvord WG, Beauchamp AE, and Smith JW 2nd. Phase II trial of interleukin 1 alpha and indomethacin in treatment of metastatic melanoma. J Natl Cancer Inst 88:44-49, 1996.

30. Holmlund JT, Kopp WC, Wiltrout RH, Longo DL, Urba WJ, Janik JE, Sznol M, Conlon KC, Fenton RG, Hornung R, Madara K, Shields MA, Smith JW 2nd, Sharfman W, Steis RG, Ewel C, Malspeis L, and Creekmore SP. A phase I clinical trial of flavone acetic acid in combination with interleukin 2. J Natl Cancer Inst 87:134-136, 1995.

31. Kopp WC, Holmlund JT, and Urba WJ. "Immunological Monitoring and Clinical Trials of Biological Response Modifiers," in Pinedo HR, Longo DL, and Chabner BA (Eds.), Cancer Chemotherapy and Biological Response Modifiers, Annual 15, Amsterdam, Elsevier Science Publishers B.V., 1994, pp. 226-286.

32. Holmlund JT, "Cytokines," in Pinedo HR, Longo DL, and Chabner BA (Eds.), Cancer Chemotherapy and Biological Response Modifiers, Annual 14, Amsterdam, Elsevier Science Publishers B.V., 1993, pp. 150-206.

33. Smith JW 2nd, Longo DL, Alvord WG, Janik JE, Sharfman WH, Gause BL, Curti BD, Creekmore SP, Holmlund JT, Fenton RG, Sznol MS, Miller LL, Shimizu MS, Oppenheim JJ, Feim SJ, Hursey JC, Powers GC, and Urba WJ. The effects of treatment with interleukin-1 alpha on platelet recovery after high-dose carboplatin. N Engl J Med 328:756-761, 1993.

34. Curti BD, Longo DL, Ochoa AC, Conlon KC, Smith JW 2nd, Alvord WG, Creekmore SP, Fenton RG, Gause BL, Holmlund JT, Janik JE, Ochoa J, Rice PA, Sharfman WH, Sznol M, and Urba WJ. Treatment of cancer patients with ex vivo anti-CD3-activated killer cells and interleukin-2. J Clin Oncol 11:652-660, 1993.

35. Holmlund JT and Schulof RS. "Cancers of the Kidney, Bladder, and Prostate," in Lokich JJ (Ed.), Cancer Chemotherapy by Infusion (2nd Ed.), Chicago, Precept Press, 1990, pp. 421-462.

36. Shields PG, Dawkins F, Holmlund J, Cohen P, and Schulof RS. Low-dose multidrug chemotherapy plus Pneumocystis carinii pneumonia prophylaxis for HIV-related Kaposi's sarcoma. J Acquired Immune Deficiency Syndromes 3:695-700, 1990.

Abstracts

1. Paoluzzi L, Gonen M, Gardner JR, Toner LE, Smith EA, Yang D, Holmlund J, Sorensen M, Manova K, O'Connor OA. Targeting Anti-apoptotic members of Bcl-2 with AT-101 in preclinical models of aggressive lymphoma in combination with cyclophosphamide (C) and rituximab (R) produces a marked improvement in therapeutic efficacy. Blood: Proc American Society of Hematology 106:680a, 2005, #2420.

2. Saleh M, Pitot H, Hartung J, Holmlund J, LoBuglio A, Forero A. Phase I trial of AT-101, an orally bioavailable inhibitor of Bcl-2, in patients with advanced malignancies. 17th AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Philadelphia, PA, November 17, 2005.

3. Lynch TJ, Raju R, Lind M, Riviere A, Gatzemeier U, Dorr A, Holmlund J, Yuen A, Sikic BI. Randomized phase III trial of chemotherapy and antisense oligonucleotide LY900003 (ISIS 3521) in patients with advanced NSCLC: initial report. Proc ASCO 2003, abstract #2504.

4. Alberts SR, Schroeder M, Cha S, Erlichman C, Steen PD, Moore DF Jr, Sargent DJ, Goldberg RM, Holmlund J. Gemcitabine and ISIS-2503 for patients with pancreatic adenocarcinoma (ACA): A North Central Cancer Treatment Group (NCCTG) Phase II study: interim analysis. Proc AACR, 2002, #LB140.

5. Ritch, P.S., Belt, R., George, S., Valdivieso, M., Figueroa, J., McCachren, S., Modiano, M., Miller, G.L. , Leonardo, J., Dorr, A., Oliver, J. W., Holmlund, J. , Otterson, G. A. and Villalona-Calero M. A. Phase I/II trial of ISIS 3521/LY900003, an antinsense inhibitor of PKC-alpha with cisplatin and gemcitabine in advanced non-small cell lung cancer (NSCLC). Proc ASCO 21:309a, 2002, #1233.

6. Melvin R Moore, Mansoor Saleh, C. M Jones, David Irwin, Radj Gervais, Robert Kerr, David Ferry, Paul Ritch, Mitchell Binder, P J Chollet, B Coudert, R Delva, Harry Raftopoulos, James Stevenson, John Wallmark, D Dunlop, Andrew Dorr, Jennifer W Oliver, Jon Holmlund.. Phase II trial of ISIS 3521/LY900003, an antisense inhibitor of PKC-alpha, with docetaxel in non-small cell lung cancer (NSCLC). Proc ASCO 2002;21:297a, #1186.

7. Emmanouilides, C. E., Saleh, A., Laufman, L., Saven, A., Harden, E., Lister, J., Moore, M., Gregory. S., Pendergrass, K., Dorr, A., Holmlund J. and Oliver J.W. Phase II trial of the efficacy and safety of ISIS 3521/LY900003, an antisense inhibitor of PKC-alpha, in patients with low-grade, non-Hodgkin's lymphoma. Proc ASCO 2002;21:282a, #1124.

8. Yuen, A. R., Halsey, J., Fisher, G. A., Advani, R., Moore, M, Saleh, M., Ritch, P., Harker, G., Ahmed, F., Jones, C. M., Polikoff, J., Keiser, W., Kwoh, T. J., Holmlund, J. T., Dorr, A., and Sikic, B. I. Phase I/II trial of ISIS 3521, an

antisense inhibitor of PKC-alpha, with carboplatin and paclitaxel in non-small cell lung cancer. Proc ASCO 20: 309a, 2001, #1234.

9. M. A. Villalona-Calero, J. Figueroa, P. Nadella, G. A. Otterson, P. Snider, K. Browning, N. P. D'Amato, R. S. Geary, J. S. Grundy, J. T. Holmlund. Phase I and pharmacokinetic (PK) study of the protein kinase C alpha (PKC-α) inhibitor ISIS-3521 in combination with cisplatin and gemcitabine in patients with solid malignancies. Published as a Supplement to Clin Can Res, Vol. 7, No. 11, Nov 2001

10. T. Dang, D.H. Johnson, K. Kelly, N. Rizvi, J. Holmlund, A. Dorr. Multicenter Phase II Trial of an Antisense Inhibitor of H-ras (ISIS-2503) in Advanced Non-Small Cell Lung Cancer (NSCLC). Proc ASCO, 2001, #1325

11. Raymond P. Perez, John W. Smith III, Steven R. Alberts, Howard Kaufman, James Posey, Paul Ritch, J. Marc Pipas, Andrew Dorr, Jon Holmlund. Phase II Trial of ISIS 2503, an Antisense Inhibitor of H-ras, in Patients (Pts) with Advanced Pancreatic Carcinoma (CA). Proc ASCO, 2001, #628

12. Mansoor Saleh, James Posey, Linda Pleasant, Al Lobuglio, Melvin Moore, Al Soltan, Andrew Dorr, Jon Holmlund. A Phase II Trial of ISIS 2503, an Antisense Inhibitor of H-ras, as First Line Therapy for Advanced Colorectal Carcinoma. Proc ASCO, 2000, #1258

13. A A Adjei, C Erlichman, J A Sloan, L J Hanson, J Reid, P Atherton, R Geary, J Holmlund, A Dorr. A Phase I Trial of ISIS 2503, an Antisense Inhibitor of H-ras in Combination with Gemcitabine in Patients with Advanced Cancer. Proc ASCO, 2000, #722

14. A.M. Oza, E. Eisenhauer, K. Swenerton, L. Elit, P. Ghatage, M. Carey, W. Faught, L. McIntosh, A. Dorr, J.Holmlund. Phase II study of c-raf kinase antisense oligonucleotide ISIS 5132 in patients (pts) with recurrent ovarian cancer - NCIC IND.116. Published as a Supplement to Clin Cancer Res, Vol 6, Nov 2000, #530

15. P. Fidias, A. Boral, G. Shapiro, A. Skarin, J. Supko, J.P. Eder Jr., J. Holmlund, A. Dorr, J. Kwoh, R. Geary, T.J. Lynch. Phase I and Pharmacokinetic Study of ISIS 5132 combined with Carboplatin and Paclitaxel for Advanced Non-Small Cell Lung Cancer. International Association for the Study of Lung Cancer, Tokyo Japan, September 2000

16. Advani R, Fisher GA, Lum BL, Halsey J, Yuen A, Holmlund JT, Kwoh TJ, Dorr A, Geary R, Sikic BI. Coagulation and Complement Effects of an Antisense Phosphorothioate Oligonucleotide Targeting Protein Kinase C-Alpha (ISIS 3521) Are Schedule and Dose Dependent. Proc ASCO 19:208a, 2000, #809

17. Jane B. Alavi, Stuart A Grossman, Jeffery Supko, Kathryn Carson, Regina Priet, Andy Dorr, Jon Holmlund. Efficacy, Toxicity, and Pharmacology of an Antisense Oligonucleotide Directed Against Protein Kinase C-Alpha (ISIS 3521) Delivered as a 21 Day Continuous Intravenous Infusion in Patients with Recurrent High Grade Astrocytomas (HGA). Proc ASCO 19, 2000, #647

18. Dorr A, Bruce J, Monia B, Johnston J, Geary R, Kwoh TJ, Holmlund J, and Nemunaitis J. Phase 1 and pharmacokinetic trial of ISIS 2503, a 20-mer antisense oligonucleotide against H-Ras, by 14-day continuous infusion (CIV) in patients with advanced cancer. Proc ASCO 18:157a, 1999, #603.

19. Gordon MS, Sandler AB, Holmlund JT, Dorr A, Battiato L, Fife K, Geary R, Kwoh TJ, and Sledge Jr GW. A phase I trial of ISIS 2503, an antisense inhibitor of H-Ras, administered by a 24-hour (hr) weekly infusion to patients (pts) with advanced cancer. Proc ASCO 18:157a, 1999, #604.

20. Holmlund JT, Rudin CM, Mani S, Fleming GF, Stadler W, Kunkel K, Kwoh TJ, Geary R, Dorr A, and Ratain MJ. Phase I trial of ISIS 5132/ODN 698A, a 20-mer phosphorothioate antisense oligonucleotide inhibitor of C-Raf kinase, administered by a 24-hour weekly intravenous (IV) infusion to patients with advanced cancer. Proc ASCO 18:157a, 1999, #605.

21. Mani S, Shulman K, Kunkel K, Geary R, Holmlund JT, Dorr A, Rudin CM, and Ratain MJ. Phase I trial of protein kinase C-α antisense oligonucleotide (ISIS 3521; ISI 641A) with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with advanced cancer. Proc ASCO 18:158a, 1999, #608.

22. Advani R, Fisher GA, Grant P, Yuen AR, Holmlund JT, Kwoh TJ, Dorr A, Geary R, and Sikic BI. A phase I trial of an antisense oligonucleotide targeted to protein kinase C-α (ISIS 3521/ISI 641A) delivered as a 24-hour continuous infusion (CI). Proc ASCO 18:158a, 1999, #609.

23. Sikic BI, Yuen A, Advani R, Fisher G, Halsey J, Geary R, Kwoh TJ, Holmlund JT, and Dorr A. A phase I trial of ISIS 3521 (ISI 641A), an antisense inhibitor of protein kinase C alpha, combined with carboplatin and paclitaxel in patients with cancer. Proc ASCO 18:445a, 1999, #1718.

24. Holmlund J, Nemunaitis J, Schiller J, Dorr A, and Kisner D. Phase I trial of C-*raf* antisense oligonucleotide ISIS 5132 (CGP 69846A) by 21-day continuous intravenous infusion (CIV) in patients with advanced cancer. Proc ASCO 17:210a, 1998, #811.

25. Nemunaitis J, Von Hoff DD, Holmlund J, Dorr A, and Eckhardt SG. Phase I/pharmacokinetic (PK) trial of a protein kinase C-α antisense oligonucleotide, ISIS 3521 (CGP 64128A), administered thrice weekly. Proc ASCO 17:211a, 1998, #812.

26. O'Dwyer PJ, Stevenson JP, Gallagher M, Mitchell E, Friedland D, Rose L, Cassella A, Holmlund J, Dean N, Dorr A, Geary R, and Yao K-S. Phase I/pharmacokinetic/pharmacodynamic trial of Raf-1 antisense ODN (ISIS 5132, CGP 69846A). Proc ASCO 17:210a, 1998, #810.

27. Sikic BI, Yuen AR, Advani R, Halsey J, Fisher GA, Holmlund J, and Dorr A. Antisense oligonucleotide therapy targeted to protein kinase C-α (ISIS 3521/CGP 64128A) by 21-day infusion: results of the phase I trial and activity in ovarian carcinomas. Proc ASCO 17:429a, 1998, #1654.

28. Marshall JL, Johnson M, Richmond E, Oberst M, Norris B, Dorr FA, and Holmlund J. A phase II trial of ISIS 3521 (CGP 64128A) in patients with refractory metastatic colorectal cancer. 10th NCI-EORTC symposium on new drugs in cancer therapy, 1998, #323.

29. Nemunaitis J, Bruce J, Mongiovi D, Weinberger K, Azad R, Monia B, Johnston J, Geary R, Kwoh J, Dorr A, and Holmlund J. Phase I trial of ISIS 2503, a 20-mer antisense phosphorothioate oligonucleotide against H-*ras*, by 14-day continuous infusion in patients with advanced cancer. 10th NCI-EORTC symposium on new drugs in cancer therapy, 1998, #324.